ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

Alexander S. Mathews
President and CEO

January 19, 2005

Division of Dockets Management
U.S. Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004D-0468 – Draft Guidance for Industry on Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-Steroidal Anti-Inflammatory Drugs for Use in Animals

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments to the Docket number 2004D-0468 requesting input on the Agency's draft Guidance for Industry #123 Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-Steroidal Anti-Inflammatory Drugs for Use in Animals.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

AHI provides the attached general and specific comments for your consideration prior to finalization of this guidance document.

Sincerely,

Alexander S. Mathews

Enclosure

2004D-0468

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Comment Form

Date	Document
January 20, 2005	GFI #123 Development of Target Animal Safety and Effectiveness Data to Support Approval of NSAIDS for Use in Animals

Commenter	Section	Paragraph Figure/ Table Line No.	Proposed Change	Comment/ Rationale
AHI	All	All	Please number the lines when publishing documents for public comment.	Line numbering clearly identifies proposed areas for change, making the commenting process easier for industry and the review of submitted comments easier for the Agency.
AHI	TOC	Labeling	Should be page 6	Typographical error
AHI	TOC	A. General Approach . . .	Should be page 6	Typographical error
AHI	TOC	2. Pain	Should be page 7	Typographical error
AHI	I. Intro	Paragraph 1, line 6	Add a comma in 6th line after the words "tissue-specific"	Clarity
AHI	II		Dosage characterization section is very confusing (or hard to follow) and rewriting of this section is recommended. The suggestions provided below may be helpful in rewriting the section.	
AHI	II	Paragraph 2, line 10.	Please incorporate a paragraph break so that 'new paragraph 3' begins with "With the enactment of ADAA,..."	Recommended change for clarity. This would separate historical information from current recommendations.
AHI	II	Paragraph 2, lines 11-12.	Reword sentence to "It is recommended, however, that sponsors characterize the critical aspects of the dosage-response relationship for those parameters relevant to the proposed indication in the new animal drug application."	Clarity.
AHI	II	Paragraphs 2 and 3.	Paragraphs need clarification on FDA's intent with regards to the sponsor characterizing the critical aspects of the dosage-response relationship.	These paragraphs currently imply that the sponsor is required to conduct dose titration studies (no longer required under ADAA) to characterize the dosage-response relationship. Please clarify.

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AHI	II	Paragraph 4, lines 3-5	If, after clarifying, the wording in current paragraph 4 (beginning with "The parameters measured..."), line 3 is intact, please change the wording from, "These parameters *should also* suggest " to "These parameters *may* suggest..."	Lines 3-5 suggest that similar variables (e.g., force plate measurements) be used in the substantial evidence studies if they were used in the dose characterization studies.
AHI	II	Paragraph 5, lines 2-6	Please delete the 2nd sentence (lines 2-6) because it is redundant and contradictory to the preceding paragraphs in Section II.	Lines 2-6 imply that the relative effectiveness of the drug must be demonstrated over the entire labeled dose range which is in contradiction with the first paragraph which states the new animal drug must be effective for the intended use at the lowest dose of a dose range whereas the upper limit of the dose range should be based on safety in the target animal.

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AHI	II		In summary, please delete Paragraphs 3, 4 and 5 and replace with the suggested new paragraph 3 as follows: "With the enactment of ADAA, dosage optimization is no longer required. It is recommended, however, that sponsors characterize the critical aspects of the dosage-response relationship for those parameters relevant to the proposed indication in the new animal drug application. The parameters measured in the characterization of the dosage or dosage range should specifically relate the proposed dosage or dosage range to the proposed indication. For some new animal drugs, this characterization information may be particularly useful for CVM to evaluate the adequacy of protocols for effectiveness studies. These parameters may suggest the appropriate study endpoints for the one or more adequate and well-controlled studies necessary to provide substantial evidence of effectiveness. Methods for gathering information to characterize the dose response relationship may include dose titration studies, pilot studies, in vitro studies, and scientific literature. Dosage characterization need not be demonstrated by substantial evidence. However, this information should be sufficient to allow qualified experts to make an informed risk-benefit assessment of the new animal drug and assure the proposed labelling is not false or misleading. Sponsors should discuss with CVM the appropriate timing for submitting information to characterize the dosage-response relationship."	A need for clarification on FDA's intent with regards to the sponsor characterizing the critical aspects of the dosage-response relationship remains, despite the proposed edits.
AHI	Section III.	Paragraph 1, line 1	Replace "ways available" with "methods"	

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AHI	III	Paragraph 3, lines 1-3	Change statement "CVM recommends that TAS studies...incorporate specific tests..., including endoscopy, to identify signs of gastrointestinal or renal toxicity." to " ..to identify signs of either gastrointestinal toxicity, such as endoscopy, or renal toxicity."	The sentence as currently stated implies that endoscopy can be used as a specific test to identify signs of renal toxicity.
AHI	III	Paragraph 3, lines 1-3	Regarding the recommendation for specific tests for gastrointestinal safety including endoscopy, please ensure clarity that specific tests such as endoscopy, for example, may be inappropriate for some species.	Species for which endoscopy is an inappropriate recommendation include, for example, small animals such as mice and rats due to size limitations and ruminants due to the interference of ingesta.
AHI	III	Paragraph 5, line 3	Remove the word "safety" from line 3 (the second to last sentence).	This sentence implies that target animal safety studies must also include additional treatment groups to factor in the fed versus fasted state over the multiples of the target dose.
AHI	V	Overall		There is no mention of pharmacodynamics at all. It is assumed that this is intentional, given the concerns expressed about the in vitro COX-1/COX-2 selectivity expressed.
AHI	V	Paragraph 1, lines 1-2.	Please change sentence to read, "CVM encourages you to provide information to describe the mechanism of action **of the drug entity** and pharmacokinetics (PK) **of the drug product."**	Clarification and recognition of the impact of formulation factors on pharmacokinetics.
AHI	V	Paragraph 1, lines 2-3	Change "establish" to "predict" or "recommend"	Pharmacokinetic data can only be used to predict or recommend dosage regimens, and only if the concentration/response relationship is known.
AHI	V	Paragraph 3, lines 4-6	Remove the following sentences: "Accordingly, recommendations associated with the generation of PK data will be highly product specific. For this reason, we encourage you to meet with CVM to discuss proposals for PK studies that may be used to support NAD approval "	While PK studies are useful for understanding dose selection, etc, PK studies are not required under NADA regulations for efficacy and safety.

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AHI	V	Paragraph 3, Line 1	Delete the words "The kinds of", and capitalize the word "Studies".	Clarity
AHI	V	Paragraph 3, line 2	Omit the words "kind of" as they are unnecessary.	Clarity
AHI	VI	general	For clarity, please state whether evidence of effectiveness for two processes (e.g., pain and inflammation) may be provided in the same study or whether separate studies should be provided.	Although the guidance states that the illustrated indications and approaches should not be construed as definitive, the examples give the impression that separate studies would be required to support an indication for control of both pain and inflammation in the same disease.
AHI	VI	Paragraph 8 ("2. Pain")	"Two indications of frequent concern are control of osteoarthritis and postoperative pain". Clarify " control of pain associated with osteoarthritis ." vs. " control of osteoarthritis..."	As noted in the Guidance Document, NSAIDs are labeled for the control of signs associated with osteoarthritis rather than control of the disease itself.
AHI	VI. B.	Paragraph 1, lines 1-2	The statement, "Cyclooxygenase-inhibiting NSAIDs generally exhibit common toxicities that may not be found during laboratory Target Animal Safety Studies . " should be changed to "*Extensive use of cyclooxygenase-inhibiting NSAIDs under conditions of use in the target species* has demonstrated that they *may exhibit infrequent* toxicities that may not be found during laboratory Target Animal Safety Studies..."	"Common" NSAID-associated toxicities are generally demonstrated in Target Animal Safety Studies. Uncommon or infrequent toxicities are sometimes identified under conditions of use rather than in Target Animal Safety Studies. Class effects may not be seen across species. Therefore, class effects should be addressed in the context of 'species'
AHI	VI. B.	Paragraph 1, lines 3-4	Please delete the statement, "CVM recommends that field studies be designed to ensure detection and documentation of adverse events."	This sentence of the Precaution Statement appears to provide a CVM recommendation for field study design and should not be included under the "Precaution Statement" on the label. CVM recommendations for demonstration of field safety and efficacy are addressed in Section IV.